Risk Factors for Drug-resistant Bloodstream Infections in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To identify risk factors for developing drug-resistant bacterial infections in patients with systemic lupus erythematosus (SLE).

Methods. A retrospective, case-control study was performed. Patients fulfilled American College of Rheumatology criteria for SLE and had an episode of bloodstream infection between 2001 and 2012. Cases were defined as those with bloodstream infection caused by drug-resistant bacteria (*Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus,* or extended-spectrum-β-lactalamase-producing *Escherichia coli*); while controls had susceptible strains of *S. aureus* or *E. coli*. Differences between groups were analyzed by Student t test or Mann-Whitney U test. Association between variables was assessed by OR (CI 95%). Multivariate analysis was performed by binary logistic regression model.

Results. Forty-four patients were included in each group. Variables associated with drug-resistant bloodstream infection were history of central nervous system activity; hematological activity, immunosuppressive treatment and prednisone dose at the time of the infection; and low C3 levels, antibiotic use, or hospitalization in the previous 3 months. In multivariate analysis, variables that remained significant were low C3 previous to infection (OR 3.12, CI 95% 1.91–8.22), previous hospitalization (OR 2.22, CI 95% 1.42–4.10), and prednisone dose at the time of infection (OR 1.10, CI 95% 1.04–1.22).

Conclusion. Low C3 levels, recent hospitalization, and prednisone dose at time of infection are independent risk factors for acquiring drug-resistant bacteria in patients with SLE. Although the present data do not fully support a change in initial treatment-decision strategies, this information could lead to prospective studies designed to address this issue, which could determine the best approach in clinical practice. (J Rheumatol First Release June 1 2014; doi:10.3899/jrheum.131261)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS BACTEREMIA GLUCOCORTICOIDS
BACTERIAL DRUG RESISTANCE COMPLEMENT SYSTEM PROTEINS INFECTION

Infections are an important cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE): 20–55% of deaths are attributable to infectious diseases. Up to 23% of hospitalizations in these patients will be secondary to infectious complications[1].

There are different risk factors, associated with both the disease and its treatment, that contribute to the development of infectious diseases in SLE. Among these, glucocorticoid use (both dose at the time of infection and cumulative dose) is considered one of the main risk factors[2,3,4,5]. Other immunosuppressive drugs, especially cyclophosphamide, have been suggested to confer risk for infections in SLE[2,3]. Immune system disorders are also involved. Patients with SLE have abnormalities, both in cellular and humoral immunity, such as defective chemotaxis, phagocytic activity, and cytokine synthesis[6,7,8]. There are also alterations in the antimicrobial action of different cellular subpopulations, such as neutrophils[9], T lymphocytes[8], and natural killer cells[10]. Further, complement deficiencies and consumption, as well as lymphopenia, may promote the development of infections[11,12,13,14]. Disease activity can also contribute, and a higher SLE Disease Activity Index (SLEDAI) score has been associated with higher frequency of infection and hospitalization due to infectious complications[15,16].

Adequate empiric antibiotic coverage for any infection leads to better outcomes related to sepsis, septic shock, and ventilator-associated pneumonias. In bloodstream infections, an optimal empiric treatment is essential. Indiscrim-

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inate antibiotic use has led to a higher prevalence of antibiotic resistance in recent years. Low-spectrum antibiotics have become less effective, making the choice of effective antibiotics more problematic. There is a higher mortality rate if the initial treatment choice is not adequate, as has been demonstrated in infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and in critically ill patients[17,18].

Different risk factors, such as previous antibiotic use and hospitalization, residence in a nursing home, and chronic dialysis, have been described for the development of drug-resistant bacteria, and use of those risk factors has been validated for initial treatment decisions. Several clinical guidelines for the management of diverse infections include immunosuppression as a risk factor; however, the type of disease or treatment that is considered immunosuppressive has not been accurately defined[19,20]. Therefore, it is important to recognize risk factors for resistant bloodstream infections in patients with SLE, which might help to develop further prospective studies aimed both to address which patients require broad-spectrum antibiotics initially, as well as to avoid indiscriminate use of those drugs.

Although infections by drug-resistant microorganisms have been considered to be relevant in terms of morbidity and mortality in patients with SLE, the role of potential risk factors in this population has not been addressed. We sought to identify risk factors associated with the development of drug-resistant bloodstream infections in SLE.

MATERIALS AND METHODS

A retrospective case-control study was performed. We included patients that fulfilled at least 4 American College of Rheumatology criteria for SLE[21], had an episode of bacterial bloodstream infection between 2001 and 2012, and were admitted to a tertiary referral center in Mexico City. Information was obtained from the hospital microbiological database and from patient records. Patients in the case group had bloodstream infection caused by drug-resistant bacteria, while patients in the control group were infected by bacterial strains responsive to treatment. Groups were matched for age (± 5 yrs) and sex. Patients were excluded if they had human immunodeficiency virus infection, organ transplantation, neoplasia, or were pregnant.

Bloodstream infection was defined as the presence of a positive blood culture and 2 criteria of systemic inflammatory response syndrome (temperature > 38°C or < 36°C, heart rate > 90/min, respiratory rate > 20/min, and leukocyte count > 12,000 or < 4000). Drug-resistant bacteria considered for study inclusion were *P. aeruginosa*, methicillin-resistant *S. aureus*, or extended-spectrum-β-lactalamase-producing *E. coli*, because a broader antibiotic coverage was required. The susceptible strains considered for the control group were ceftazidime-sensitive *E. coli* and methicillin-sensitive *S. aureus*.

Variables recorded for each patient were age, sex, comorbidities, time from SLE diagnosis and history of SLE activity; disease activity measured by SLEDAI score[22], anti-dsDNA antibodies, complement fraction (C3 and C4) levels, leukocyte and lymphocyte counts in the 3 months prior to and at the time of diagnosis of infection; as well as immunosuppressive treatment in the previous year and at the time of infection. The prednisone dose over the previous year was calculated as an average of the daily dose throughout those 12 months, based on clinical records. Also, it was registered whether the patient was in hemodialysis, had used antibiotics, or had been hospitalized in the 3 months preceding infection (so it would be considered healthcare-associated), or whether the infection had been nosocomial (acquired after 48 h of hospitalization).

Statistical analysis. Variables are expressed as mean and SD, or as median and interquartile range or proportions, as appropriate. Differences between groups were analyzed by Student t test or Mann-Whitney U test. Association between variables was assessed by chi-square test and OR (95% CI). Multivariate analysis was performed by binary logistic regression model and expressed as OR. The variables included in the multivariate analysis are fully detailed below. A p value < 0.05 was considered statistically significant, unless stated otherwise. Statistical analysis was performed using SPSS software, version 21.

RESULTS

Eighty-eight subjects were included, 44 in each group. Ages ranged from 16 to 73 years; the mean age for cases was 37.06 ± 14.4 years versus 37.7 ± 14.1 years for the control group. Most patients were female (93.1%). In the year preceding infection, 90.9% of patients in the case group and 79.5% in the control group received immunosuppressive treatment, while 93.1% of cases and 75% of controls were under immunosuppressive therapy at the time of the infection. Glucocorticoids were the most common immunosuppressive drug used. In the year before infection, 81.8% of cases and 77.2% of controls received glucocorticoids. Cyclophosphamide use was found in 15.9% of patients in each group in the year before the infectious event. Hydroxychloroquine was part of the treatment in 13.6% of cases and 20.4% of controls; however, it did not confer protection for acquiring drug-resistant bacteria (OR 0.44, 95% CI 0.148–1.33, p = 0.229). No patient had received rituximab or other biologic therapies.

As for bloodstream infections, in the case group 40.9% were caused by *P. aeruginosa*, 34.1% by *S. aureus*, and 25% by *E. coli*; in the control group, 59% by *E. coli* and 41% by *S. aureus*. The documented origin sites of bloodstream infections were intravenous catheter (31.8% in cases and 22.7% in controls), respiratory tract (27.2% in cases and 4.5% in controls), urinary tract (13.6% in cases and 43.1% in controls), skin and soft tissue (13.6% in cases and 15.9% in controls), intraabdominal cavity (6.8% in cases and 4.5% in controls), and gastrointestinal tract (2.2% in both groups).

Table 1 shows characteristics regarding SLE activity, anti-dsDNA positivity, complement levels, and history of hospitalization and antibiotic use. Patients with drug-resistant bloodstream infections had higher SLEDAI scores and anti-dsDNA levels in the 3 months prior to the infection. After univariate analysis, the following variables were found to be associated with development of drug-resistant bacterial bloodstream infections: history of central nervous system activity; low C3 levels, antibiotic use and hospitalization in the 3 months prior to infection; hematologic activity, immunosuppressive treatment and prednisone dose at the time of the infection; as well as nosocomial infection (Table 1).

Particularly, we analyzed prednisone dose at the time of infection and as an ordinal variable, dividing it into

Table 1A. Clinical features of the study population.

Feature (Continuous)	Cases, Mean ± SD	Controls, Mean ± SD	p
Variables assessed prior to infection			
Prednisone dose, mg/day	22.33 ± 2.84	15.51 ± 2.39	0.07
SLEDAI score	14.63 ± 2.02	7.6 ± 1.29	**0.005**
Anti-dsDNA, U/ml	599.60 ± 197.8	129.44 ± 38.98	**0.026**
Variables assessed at the time of infection			
Time since SLE diagnosis, mos	122.14 ± 19.29	134.41 ± 17.14	0.636
Prednisone dose, mg/day	35.68 ± 3.70	14.94 ± 2.45	**0.002**
SLEDAI score	7.7 ± 1.23	6.39 ± 1.03	0.429
Anti-dsDNA, U/ml	117.96 ± 47.99	70.52 ± 42.89	0.477

Values highlighted in bold represent statistically significant p values. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 1B. Clinical and serologic features of the study population.

Feature (Categorical)	OR	95% CI	p
History of disease activity			
Lupus nephritis	1.17	0.89–1.53	0.345
Hematological activity	1.01	0.48–2.06	0.597
CNS activity	2.66	1.15–6.17	**0.025**
Disease activity at time of infection			
Lupus nephritis	1.15	0.62–2.13	0.41
Hematological activity	2.11	1.07–4.14	**0.038**
CNS activity	1.01	0.89–1.11	0.484
Other variables prior to infection			
Immunosuppressive treatment (12 mos)	1.14	0.95–1.36	0.229
Positive anti-dsDNA, U/ml	1.03	0.41–2.58	0.542
Low C3 levels, mg/dl	2.71	1.25–5.9	**0.008**
Lymphopenia, < 1000/ml	1.17	0.81–1.63	0.519
Antibiotic use	2.18	1.43–3.32	**< 0.001**
Hospitalization	2.9	1.61–5.2	**< 0.001**
Hemodialysis	1.66	0.81–3.4	0.231
Other variables at time of the infection			
Immunosuppressive treatment	1.24	1.02–1.05	**0.039**
Prednisone dose			
0 mg/day	0.32	0.09–0.54	0.607
< 7.5 mg/day	1.12	0.98–2.32	0.072
7.5–30 mg/day	2.22	1.50–3.92	**0.02**
> 30 mg/day	7.14	2.69–18.99	**0.001**
Positive anti-dsDNA, U/ml	1.12	0.63–1.4	0.506
Low C3 levels, mg/dl	1.92	0.93–3.96	0.098
Lymphopenia, < 1000/ml	1.09	0.80–1.23	0.604
Nosocomial-acquired infection	2.77	1.46–5.2	**0.001**

Values highlighted in bold represent statistically significant p values. CNS: central nervous system.

subgroups: no prednisone, low dose (up to 7.5 mg/day), medium dose (up to 30 mg/day), and high-dose (over 30 mg/day). In this regard, the medium dose (OR 2.22, 1.50–3.92, p = 0.020) and high dose (OR 7.14, 2.69–18.99, p = 0.001) were associated with the highest risk, as displayed in Table 1.

Variables found to be significant in univariate analysis as mentioned, as well as those that could be of clinical relevance (time since SLE diagnosis, SLEDAI score, dsDNA levels 3 months prior to and at the time of infection, history of lupus nephritis, and endstage renal disease), were included in the multivariate analysis. After binary logistic regression analysis, the risk factors that remained significant were low C3 levels (OR 3.12, CI 95% 1.91–8.22), previous hospitalization (OR 2.22, CI 95% 1.42–4.10), and prednisone dose at the time of infection (OR 1.10, CI 95% 1.04–1.22), as displayed in Table 2.

DISCUSSION

Because infections are an important complication in SLE[1],

Table 2. Multivariate analysis. Risk factors associated with drug-resistant bacterial bloodstream infections in patients with systemic lupus erythematosus.

	OR	95% CI	p
Low C3 levels previous to infection	3.12	1.91–8.22	0.022
Hospitalization previous to infection	2.22	1.42–4.1	0.003
Prednisone dose at the time of infection	1.10	1.04–1.22	0.001

it is fundamental for these patients to receive adequate treatment. Achieving an optimal antibiotic coverage initially is essential to improve patient outcomes. The aim of our study was to assess risk factors specific to patients with SLE for developing bloodstream infections caused by drug-resistant bacteria, which potentially require broad-spectrum antibiotic coverage and timely treatment initiation.

Bloodstream infections were studied because that minimized the possibility of contamination, as could happen in cultures obtained from other sites. Moreover, these are serious infections, with a high mortality rate (76% survival at 30 days and 67% at 360 days, as observed by Chen, *et al*[23]). Therefore, it is particularly relevant to have an adequate initial treatment.

In our present work, different risk factors were found, some of which are in agreement with those reported for the general population, such as history of hospitalization (3 mos prior to bloodstream infection)[19]. Others were specifically related to SLE and its treatment. These data support the hypothesis that patients with SLE have particular characteristics, which not only increase the individual's susceptibility to infectious complications, but also to the development of resistant microorganisms that require initial broad-spectrum antibiotic coverage.

An element considered by expert consensus and treatment guidelines as an indication to initiate a broad-spectrum antibiotic coverage is immunosuppression, whether it is secondary to a disease or a specific therapy[19,20]. Patients with SLE have both elements, because both intrinsic alterations in the immune system and the drugs employed in their treatment confer a certain degree of immunosuppression.

Although an association seems obvious, even the best available evidence about the role that different immune system abnormalities and immunosuppressive therapies play in the development of drug-resistant infections appears to be quite scant. Shorr, *et al* studied a cohort of 639 hospitalized patients with pneumonia and examined the risk factors for drug-resistant bacteria as the etiologic agent. Although a larger number of patients considered to be immunosuppressed had resistant bacteria, it was not found to be a significant risk factor[24]. In a case-control study, Nseir, *et al* included all patients admitted to an intensive care unit during a 2-year period (n = 256), and did not find an association between immunosuppression and drug-resistant infections[25]. Finally, Aliberti, *et al* studied 935 patients with community-acquired pneumonia and also did not find immunosuppression to be an independent factor for resistant bacteria[26]. In these 3 studies, the most relevant factors were previous antibiotic use and health-system contact. It is important to emphasize the different operational definitions of "immunosuppression," because diverse diseases and therapies were considered.

Because of the absence of strong evidence and in view of the different definitions for immunosuppression, it is warranted to identify potential risk factors, considered to be specific to patients with SLE, particularly if we take into account the heterogeneous nature and clinical spectrum of SLE. This highlights the relevance of our findings, in which, at least to our knowledge, SLE-specific risk factors for drug-resistant infections are described for the first time.

Regarding antimalarials, they have been found to be inversely associated with major infections in patients with SLE[5]. We did not find a protective effect of hydroxychloroquine against drug-resistant bacteria. However, there was a trend for it to be protective, and the remarkably low number of patients receiving this drug could account for the lack of difference between both groups.

A novel finding was that low C3 levels were an independent risk factor for development of drug-resistant bacterial infections. The role of complement, and specifically C3, in microorganism eradication has been widely demonstrated. By means of its functions in opsonization, phagocytosis enhancement, and promotion of inflammation, C3 is able to regulate innate and adaptive immunity. Although classically its use against extracellular bacteria has been considered its main role[12], the importance of C3 in controlling infections by intracellular microorganisms, such as *Chlamydia psitacci*, has also been proven[27]. Another example of the relevance of C3 in the immune response is the study by Yuan, *et al*, in which septic peritonitis was induced in mice. An early administration of exogenous C3 was associated with a diminished bacterial load and less inflammatory damage to the liver and kidney, as well as a higher survival rate[28].

In addition, O'Brien, *et al* studied C57BL/6 mice and demonstrated that the complement response toward the influenza virus changed according to the viral strain. C3 levels were higher when mice were exposed to H5N1 virus (aviary influenza) than when they were exposed to the

H1N1 (pandemic) or seasonal strains. Disproving the initial hypothesis, mice with higher C3 levels did not show more tissue damage; and they had a more efficient viral elimination and less inflammation than those C3-/- [29]. This demonstrated the relevance of the complement system, and specifically of C3, in immune system activation and regulation. It also exemplifies the different roles and responses C3 may have when encountering different microorganisms with similar characteristics. The aforementioned data are in agreement with our findings, in which low C3 was a risk factor for infections by certain types of bacteria.

Further, different elements of the complement system have been associated with infections by drug-resistant bacteria. In a study by Ramos-Sevillano, *et al*, complement was found to work along with antibiotics to eliminate drug-resistant bacteria. When *S. pneumoniae* resistant strains were exposed to subinhibitory doses of cefditoren and ceftriaxone, complement activation was enhanced through C1q and C3b deposition[30].

It has also been demonstrated that biofilms, which are strongly associated with catheters, prostheses, and medical instruments, induce complement evasion mechanisms[31,32]. Biofilms significantly promote bacterial persistence and antibiotic resistance, specifically through decreased C3b deposition. This emphasizes the role of complement proteins in biofilm bacterial control and elimination. In our study population, this could be especially relevant for patients with indwelling catheters, which are related to biofilm formation. In the drug-resistant bacteria group, 34% of patients were receiving hemodialysis, and in 31.8% of them, infections were related to intravenous catheters. According to current evidence, our results suggest that low C3 levels may contribute to inadequate local control of those resistant bacteria, promoting the development of systemic infections.

Our study has several limitations. It is a retrospective investigation performed in a single center. Also, the role of hydroxychloroquine could not be adequately assessed because of the low percentage of patients taking this drug. Further prospective research is required to validate our findings and assess whether our data can be applied to other populations, and specifically to other clinical settings in which antibiotic-resistance patterns and SLE patient characteristics may be different.

For patients with SLE, in addition to recent hospitalization, low C3 levels constitute an independent risk factor for acquiring drug-resistant bacterial bloodstream infections. Although the present data do not fully support a change in initial treatment-decision strategies, this information could lead to prospective studies specifically designed to address this issue, which could determine the best approach in clinical practice. Thus, outcomes of one of the most common complications in patients with SLE may improve, and at the same time, unnecessary use of broad-spectrum antibiotics, and consequently, drug-resistance, could be limited.

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